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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,105	03/07/2000	ZIVA MESSIKA	MESSIKA=2	9465

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EXAMINER
SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/15/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,105	MESSIKA ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to the amendment and response filed on 1/29/02 in Paper No: 9. Claims 7-12 have been added. Therefore, claims 1-12 are pending.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

3. The oath and declaration has been corrected.

35 USC § 112, second paragraph rejections withdrawn

4. Applicant's amendments have obviated the rejection regarding vague and indefinite language used in claims 1, 2, and 6. Specifically, applicant has changed the term biologically active or physiologically active to cytotoxic biological activity.

5. Amendments have obviated the rejection regarding vague and indefinite language use in claim 2. The claim has been amended to read "mutant". In addition, applicant has placed activity limitations on this mutant.

6. Amendment's and arguments have also obviated the rejection regarding vague and indefinite language used in claims 5 and 6 with respect to "effective amount".

Claim Rejections

7. Newly added claims 7-12 contain subject matter present in previously rejected claims 1-6. Applicant's arguments filed on 1/29/02 in Paper No: 9 in reference to claims 1-6 have been fully considered but are not persuasive.

Claim Rejections - 35 USC § 112, first paragraph

8. The rejection of claim 2 for lack of written description and enablement is withdrawn in light of the amendment to claim 2 (changed from variant to mutant). However, newly added claim 7 recites the same limitation of "variant thereof" thus the 112, first paragraph rejections pertaining to lack of written description and lack of enablement are applied for the reasons stated in Paper No: 8.

Claim Rejections - 35 USC § 112, second paragraph

9. Claim 2 is rejected as vague and indefinite for reciting the term "capable". Claims 3, 4 and 7-12 are rejected insofar as they depend on claim 2.

10.Claim 7 is rejected as vague and indefinite for reciting the term "variant", because the term "variant" is not defined in the specification. This is because a variant may encompass a single amino acid change or several amino acid changes and it is unclear what "variants" are encompassed in this claim. Claims 8 and 9 are rejected insofar as they depend on claim 7.

Claim Rejections - 35 USC § 102,

11. The rejection of claims 1, 2 and 4 under 35 U.S.C. § 102(b) as anticipated by Korn et al (1988) is maintained. In addition, newly added claims 7 and 12 are also rejected under 35 U.S.C. § 102(b) as anticipated by Korn et al.

Applicant argues that the TNF isolated in Korn et al. is denatured. However, as indicated in Korn et al. (page: 354), only the material which was immunoprecipitated and run on the SDS gel is denatured. Korn et al. demonstrated the cytotoxic activity of TNF produced by the cells. The TNF activity was demonstrated by removing the

supernatant from the transfected CHO clones and applying it to human fibroblast SV80 cells (see Table: 1).

Although Korn et al. do not explicitly state that the TNF produced by the CHO cells is glycosylated, it is well known in the art that the mammalian cells like CHO cells provide post-translational modifications to protein molecules including glycosylation (see pages: 7 and 8 of Paper No: 8). It is widely recognized in the art that mammalian cells glycosylate proteins (see Patent No: 5, 695, 953). Furthermore, Fransen et al. (1985) describe the molecular cloning and expression of biologically active TNF which are glycosylated. In addition, Jue et al. (1990) also describe a glycosylated TNF/cachectin. This supports the assertion in the previous office action that TNF produced by CHO cells is glycosylated. Applicant has not provided any evidence that TNF produced by CHO cells is not glycosylated. Therefore, the claims of the instant application are anticipated by Korn et al.

12. Claims 1, 2, 4 and 7-12 are also rejected under 35 U.S.C. 102(b) as being anticipated by Nakagawa et al. (1991).

The instant invention is directed to glycosylated human tumor necrosis factor protein.

Nakagawa et al. teaches the method for producing biologically active human tumor necrosis factor (TNF-β) or human lymphotoxin (LT) protein in Chinese hamster ovary (CHO) cells. There is no difference between the method disclosed in Nakagawa et al. and the one described in the present application in producing the recombinant TNF using CHO cells. Furthermore, the human tumor necrosis factor-β (human

lymphotoxin) produced in the CHO cells was glycosylated (abstract). They also demonstrated the biological activity of the protein in LT-sensitive L-929 mouse fibroblast cells. Therefore, the disclosure of Nakagawa et al. anticipates claims 1, 2, 4 and 7-12.

Claim Rejections - 35 USC § 103,

13. The rejection of claims 3, 5 and 6 under 35 U.S.C. § 103(a) as being unpatentable over Korn (1988) in view of Allet (U.S. Patent No: 5,487,984) is maintained. In addition, newly added claims 8-11 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Korn in view of Allet.

Applicant claims that the TNF produced by Korn et al. is inactive. However, as indicated above in paragraph 9, the TNF produced by the CHO cells is glycosylated and active. Furthermore, applicant claims that Allet states that the mature human TNF is not glycosylated. Regardless of the speculation by Allet of the glycosylation state of TNF, the Allet reference was introduced by the Office to describe the purification of TNF (column 6, lines 61-67), compositions and treatment of human diseases (column 7, lines 35-43, and column 12, line 4, to column 13, line 5). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods disclosed in Korn et al. to produce and purify the glycosylated TNF protein, obtain compositions and use it in treating human disease as taught by Allet et al. One of ordinary skill would have been motivated with reasonable expectation of success to modify the methods of Korn et al. because Allet et al. teach that recombinant TNF can be purified and formulated into compositions for treatment of human diseases (column

6, lines 61-67; column 7, lines 35-43 and column 12, line 4 to column 13, line 5). Therefore, the instant invention is *prima facie* obvious over Korn et al. (1988) in view of Allet et al. (U.S. Patent No: 5,487,984). It should be noted that although Korn et al. did explicitly state that TNF was glycosylated , they did recognize the therpeutic value of the preparation (page: 357). In addition, glycosylation is a known property of expression in mammalian cells like CHO cells and thus is not an unexpected result of the present invention.

14. Claims 3, 5, 6 and 8-11are also rejected under 35 U.S.C. 103(a) as being unpatentable over Nakagawa et al. (1991) in view of Allet et al. in (U.S. Patent No: 5,487,984).

The instant invention is directed to purifying glycosylated human tumor necrosis factor protein, pharmaceutical compositions and methods of treatment.

The relevance of Nakagawa et al. has been set forth above in paragraph 10. Nakagawa et al. teaches a method for producing biologically active human tumor necrosis factor (TNF-β), also known as human lymphotoxin (LT) protein, in Chinese hamster ovary (CHO) cells. However, they do not describe the purification of the glycosylated TNF or the use of the same in treatment of human diseases.

Allet et al. describe the purification of TNF (column 6, lines 61-67), pharmaceutical compositions and treatment of human diseases (column 7, lines 35-43, and column 12, line 4, to column 13, line 5). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods disclosed in Nakagawa et al. to produce and purify the glycosylated TNF protein, obtain

pharmaceutical compositions and use it in treating human disease in combination with the teachings of Allet et al. One of ordinary skill would have been motivated with reasonable expectation of success to modify the methods of Nakagawa et al. because Allet et al. teach that recombinant TNF can be purified and formulated into compositions for treatment of human diseases (column 6, lines 61-67; column 7, lines 35-43, and column 12, line 4, to column 13, line 5). Therefore, the instant invention is *prima facie* obvious over Nakagawa et al. (1988) in view of Allet et al. (U.S. Patent No: 5,487,984).

15. No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JEFFREY STUCKER
PRIMARY EXAMINER